Original Research
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Is bad breath associated with dyspepsia? An association and an equivalence study

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Abstract: Halitosis affects all populations worldwide. The presence of chronic halitosis may be related to a health problem. Patients with bad breath usually seek a gastroenterologist and, in some cases, invasive and expensive exams, such as digestive endoscopy, are performed to investigate the etiology of halitosis. This study aimed to investigate whether the prevalence of bad breath in patients diagnosed with dyspepsia (any pain or discomfort in the upper abdomen) is higher than or equivalent to that in non-dyspeptic patients. This is a cross-sectional study that included 312 patients from university hospitals in the city of Rio de Janeiro (141 dyspeptic patients and 171 non-dyspeptic ones). The presence of halitosis was defined based on different cutoff points. Association analyses were performed using a log-binomial model and 95% confidence intervals were calculated for the coefficients, adjusting for sex and age. The equivalence test (Westlake) was used to test the hypothesis of equivalence between the proportions of patients with bad breath in the two groups (dyspeptic vs. non-dyspeptic), considering an equivalence band of ± 15%. The prevalence of bad breath ranged from 30% to 64% according to the definition of bad breath. Dyspepsia was not associated with bad breath in any of the three definitions of bad breath (two specific ones and a sensitive one). The proportion of patients with marked bad breath was equivalent in patients with and without dyspepsia.

Keywords: Mouth Breathing; Stomach Diseases; Therapeutic Equivalency

Introduction

Halitosis (bad breath) is a frequent complaint that affects about 14% to 30% of the population, with important consequences for personal and social life.[1] There are two possible etiologies of bad breath: extraoral and intraoral. Oral etiology cases comprise the vast majority,[2] but 10–13% of cases are due to extraoral etiology, and about 1% of this percentage comes from gastrointestinal disorders. Oral problems related to pathologies or poor oral hygiene would be the main causes of bad breath, associated with approximately 90% of bad breath cases.[3-5] To investigate the source of extraoral halitosis, patients are referred to different specialists to investigate several possible disorders, such as tonsillitis or chronic sinusitis, gastroesophageal reflux, gastric inflammatory processes,

Zenker's diverticulum, or gastrocolic fistula, liver failure, cirrhosis, diabetes, trimethylaminuria, bronchiectasis, lung abscesses, and renal failure.[6-9]

Regarding the relationship between bad breath and dyspepsia (any pain or discomfort in the upper abdomen), a prospective study found a high frequency of bad breath in patients with dyspepsia and some relationship between bad breath and symptoms such as regurgitation, nausea, and abdominal distention. However, no association was detected between endoscopic findings and bad breath.[10] The gram-negative bacterium *Helicobacter pylori (H. pylori),* a major urease producer and a frequent target of investigations in recent decades, seems to be associated with bad breath.[6, 11-13] There was a higher frequency of bad breath in dyspeptic patients with *H. pylori* infection than in those without it.[14, 15] The percentage of patients with bad breath with *H. pylori* infection was close to 40%, but less than 10% in those without the infection.[13]

Studying the magnitude of the prevalence of halitosis in patients with or without dyspepsia can guide clinicians and patients on the most likely causes of extraoral bad breath. Considering that the suspicious presence of bad breath has been one of the reasons that lead patients to seek gastroenterologists and even to undergo digestive endoscopy, which is an invasive and costly examination, it is important to establish whether digestive disorder, organic or functional, is associated with bad breath.

We hypothesized that the proportions of bad breath cases in patients with dyspepsia and in the general population would be equivalent. This study aimed to investigate whether the prevalence of bad breath in patients diagnosed with dyspepsia (any pain or discomfort in the upper abdomen) is higher than or equivalent to the prevalence in non-dyspeptic patients.

Methodology

This was a cross-sectional study of patients treated at two university hospitals in the city of Rio de Janeiro – Hospital Universitário Pedro Ernesto (HUPE) and Hospital Universitário Gaffrée Guinle (HUGG). At HUPE, where patients diagnosed with dyspepsia were recruited, data collection took place at the Endoscopy Unit between March 1, 2006 and February 28, 2007, and involved patients clinically diagnosed with dyspepsia and referred for digestive endoscopy. During the data collection at HUPE, the bad breath of patients and their chaperones was measured; however, the chaperones' data were not used in the present study. At HUGG, where the comparison group patients were recruited, data were collected from patients who underwent examinations between January 1 and February 28, 2007 at the Clinical Pathology Laboratory. The data were collected during the doctoral studies of one of the authors (NCPR). Patients recruited for the study had been referred from HUGE (from different outpatient sectors of the hospital) for routine blood tests at the Clinical Pathology Laboratory.

The eligibility criteria for this study were: age of 18 years or older, nonsmoking, no use of antibiotic therapy in the past four weeks, and morning tests after a 12-hour fasting period.

The sample size calculation was based on the equivalence test.[16-18] To calculate the number of individuals in each group, we considered halitosis to affect 30% of patients in both groups, a maximum difference limit of 15%, a study power of 80%, and a one-sided 95% confidence interval (95% CI), which required at least 116 participants in each comparison group.

The dependent variable (outcome), bad breath, was measured by organoleptic evaluation of the mouth air by a trained evaluator (NCPR). The participant was instructed to count to 10 while the evaluator's nose was positioned approximately 20 cm away from the participant's mouth during the count. Halitosis was scored as follows: 0 = absence of halitosis or very good breath; 1 = mild halitosis or good breath; 2 = moderate or average halitosis; 3 = severe halitosis or strong malodor; and 4 = very severe halitosis or very strong malodor. Three definitions (two specific ones and a sensitive one) of the presence of bad breath were used,: 1) specific cutoff (SP): the presence of bad breath included "severe" and "very severe" scores; 2) specific cutoff that excluded the "moderate" score (SP-EMS): the

presence of bad breath included "severe" and "very severe" scores, excluding participants with moderate scores. 3) sensitive cutoff (SE): the presence of bad breath included "moderate", "severe," and "very severe" scores.

The exposure of interest (dyspepsia) was defined as any pain or discomfort in the upper abdomen.

Exposed participants were patients from the gastroenterology outpatient clinic of HUPE clinically diagnosed with dyspepsia by gastroenterologists and referred for digestive endoscopy. The comparison group consisted of patients from different outpatient sectors of the hospital referred by physicians for routine blood tests at the HUGG's clinical pathology laboratory.

A single evaluator (NCPR) performed the organoleptic evaluation of bad breath. Before data collection, training and calibration were carried out by the evaluator who performed the organoleptic evaluation.

Blinding of the outcome evaluator was implemented only in the dyspepsia-exposed group for logistic reasons. In the exposed group, the presence of a chaperone was mandatory for the patient to undergo the examination. Therefore, blinding was implemented by measuring the oral odor of patients and chaperones, without the evaluator knowing whether the examinee was the patient or the chaperone. In the comparison group, the presence of chaperones for accompanying the patients during routine exams in the clinical pathology laboratory was not mandatory; therefore, it was not possible to implement the same blinding strategy.

Information about sex and age was obtained from all participants. Information on test results (urease and endoscopy) and on comorbidities and self-reported symptoms (diabetes, hypertension, hypercholesterolemia, lung disease, heart disease, liver disease, kidney disease, gastrointestinal disease, sinusitis, rhinitis, pharyngitis, diarrhea, flatulence, constipation, and xerostomia) was collected among patients with dyspepsia for better description of the exposed population.

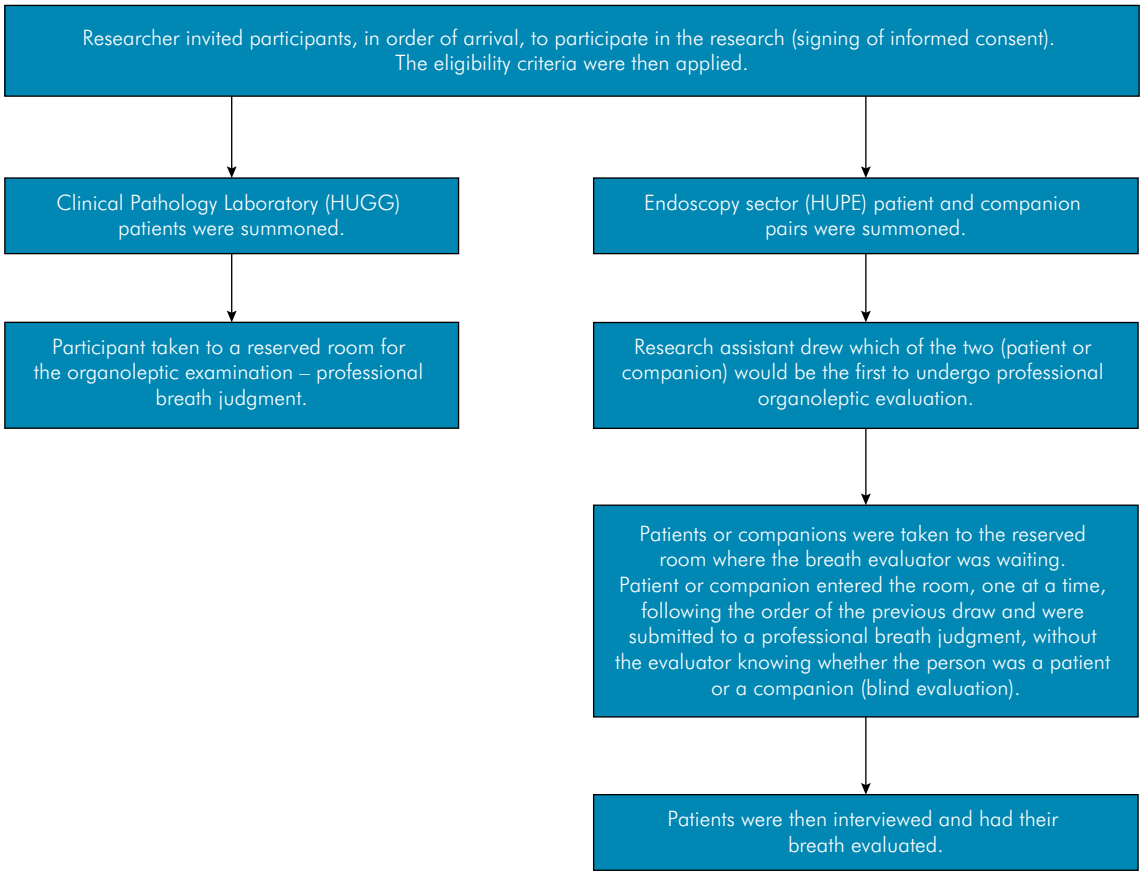
The research steps are shown in detail in Figure 1.

In association study, when the null hypothesis is not rejected, that does not indicate equivalent proportions, but rather a lack of evidence to reject that proportions are equal in the groups (32). In contrast, equivalence studies indicate whether the proportions are similar in the two comparison groups, but require narrow differences, defined through an equivalence margin, which demands a large sample size. It is possible to conclude that the proportions are equivalent when the confidence interval estimated in the test is within the pre-established equivalence margin.[19-22]

In data analysis, means and proportions were reported to describe the profile of participants. In the superiority trial, we used a log-binomial model for simple and adjusted analyses. The choice of the log-binomial model was based on the effect measure resulting from the model, the prevalence ratio, which, unlike the odds ratio, does not overestimate the effect measure in the presence of frequent events, such as halitosis.[23,24] The model's results are interpreted as a prevalence ratio, that is, to what extent the prevalence in the exposed group is higher or lower than that in the unexposed group. We estimated prevalence ratios (PRs) and their respective 95% CIs. The variables included in the model were: dependent variable (outcome) – bad breath, and independent variables (exposures) – dyspepsia, sex, and age. In the equivalence study, the proportion of bad breath in each group and the respective 95% CIs were initially estimated, as well as the difference between the two proportions. The equivalence test (Westlake) was then used to test the hypothesis of equivalence between bad breath proportions in the two groups, considering the equivalence margin of ±15% (interval on which the two bad breath proportions were considered equivalent). Other statistical tests were performed for the one-sided hypotheses, and the CI of the equivalence test was estimated.

Graphic models were used to supplement the analysis. All analytical procedures were performed using the R-Project statistical program (version 4.1.1).

This research was approved by the Research Ethics Committee of the Instituto de Medicina Social, Universidade do Estado do Rio de Janeiro, on July 5, 2005.



HUPE: Hospital Universitário Pedro Ernesto (patients with dyspepsia and their chaperones); HUGG: Hospital Universitário Gaffrée Guinle (comparison group patients).

Figure 1. Flowchart of data collection phases.

Results

The total number of eligible patients was 312 (141 exposed to dyspepsia and 171 in the comparison group). The mean age of the participants was 53.93 years (standard deviation – SD = 15.21). Among the patients with dyspepsia, the mean age was 53.86 (SD = 14.66), while in the comparison group the mean age was 53.99 (SD = 15.71). The percentage of male participants was 28.85% (SD = 45.38) – 35.50% and 23.40% in the dyspepsia and comparison groups, respectively.

Among the participants with dyspepsia and comorbidities, 42.40% were hypertensive, 21.20% had hypercholesterolemia or lung disease, 37.30% had flatulence, and 23.70% had constipation. The urease test for detection of *H. pylori* was positive for 49.04%. Endoscopy indicated chronic gastritis in 26.80% (Table 1).

The proportions of individuals with bad breath were 31%, 45%, and 63% according to the specific (SP), specific excluding moderate score (SP-EMS), and sensitive (SE) criteria, respectively. Halitosis proportions were similar between patients with and without dyspepsia (30% vs. 35% using SP criteria) (Table 2).

Both in unadjusted and adjusted analyses, there was no association between dyspepsia and bad breath, nor between bad breath and the variables sex and age (Table 3).

Table 4 shows that the one-sided hypotheses were not significant in any of the definitions of bad breath, i.e., it was not possible to rule out the hypothesis of equality between the proportions. The narrowest 95% CI was observed in the SP and

Table 1. Characteristics of the patients clinically diagnosed with dyspepsia.

Variable	Cases	% (95% CI)
Self-reported comorbidities and symptoms (n = 118)		
Diabetes	9	7.6 (2.77–12.49)
Hypertension	50	42.4 (33.33–51.42)
Hypercholesterolemia	25	21.2 (13.70–28.67)
Lung disease	25	21.2 (13.70–28.67)
Heart disease	12	10.2 (4.64– 15.70)
Liver disease	16	13.6 (07.29–19.83)
Kidney disease	16	13.6 (07.29–19.83)
Gastrointestinal disease	42	35.6 (26.83–44.36)
Sinusitis	18	15.3 (08.67–21.84)
Rhinitis	13	11.1 (5.33–16.89)
Diarrhea	22	18.6 (11.51–25.77)
Flatulence	44	37.3 (28.43–46.14)
Constipation	28	23.7 (15.94–31.52)
Xerostomia	14	14.4 (59.22–84.84)
Exam results		
Positive urease (n = 104)	51	49.04 (39.27–58.81)
Endoscopy (n = 97)		
Normal	25	25.77 (16.91–34.63)
Chronic gastritis	26	26.80 (17.83–35.78)
Hiatal hernia	12	12.37 (5.70–19.04)
Others	34	35.05 (25.39–44.72)

CI: Confidence interval.

SP-EMS definitions of bad breath, in which the two proportions were shown to be equivalent. In the SE definition of bad breath, there was no equivalence between the proportions.

Figure 2 illustrates the equivalence test result, considering the three definitions of bad breath. The prevalence rates of halitosis in the non-dyspeptic group within the equivalence band (±15%) are plotted on the x axis. The 95% CI of the bad breath proportion in the dyspeptic group was plotted over the area of this equivalence margin. Only the 95% CI of the SE definition criteria exceeds the upper or lower bounds defined for the equivalence margin (Figure 2).

Table 2. Distribution of bad breath between outpatients diagnosed with dyspepsia and a comparison group according to different cutoff points for defining the presence of bad breath in adults evaluated in the morning after a 12-hour fasting period.

Bad breath definition criteria	n	Bad breath proportion (%)	95%CI
SP			
Dyspepsia	141	30	23–38
Comparison	171	35	28–42
SP-SEM			
Dyspepsia	94	46	35–56
Comparison	137	44	35–52
SE			
Dyspepsia	141	64	56–72
Comparison	171	55	47–63

n: Number; CI: confidence interval; SP: specific cutoff point: very severe or severe vs. moderate or mild or absent halitosis (n = 312); SP-EMS: specific cutoff point excluding moderate score: very severe or severe vs. mild or absent halitosis (n = 231); SE: sensitive cutoff point: very severe or severe or moderate vs. mild or absent halitosis (n = 312).

Discussion

Our main finding was that the prevalence of bad breath was similar between patients diagnosed with dyspepsia and the comparison group. This finding suggests that dyspepsia did not contribute to bad breath. When we made the comparison using the sensitive definition of bad breath, *i.e.*, including the moderate score, the prevalence increased in both groups, without any evidence of a difference between the groups. This finding suggests that, in our sample, dyspepsia-related gastric problems may have caused a noticeable odor in the breath (moderate or average halitosis), but not to the point of causing bad breath (strong or very strong malodor). Scientific studies on the prevalence of bad breath in individuals with gastrointestinal disorders are rare, but they corroborate our results and question the universal belief of an association between gastrointestinal disorders and bad breath.[2,25,26] On the other hand, previous studies have shown consistency regarding the association of bad breath with local oral problems.[2,11,27-30] The questionable relationship between digestive problems and bad

Table 3. Unadjusted and sex- and age-adjusted estimates of the association between dyspepsia and bad breath according to different cutoff points for bad breath definition in adults evaluated in the morning after a 12-hour fasting period.

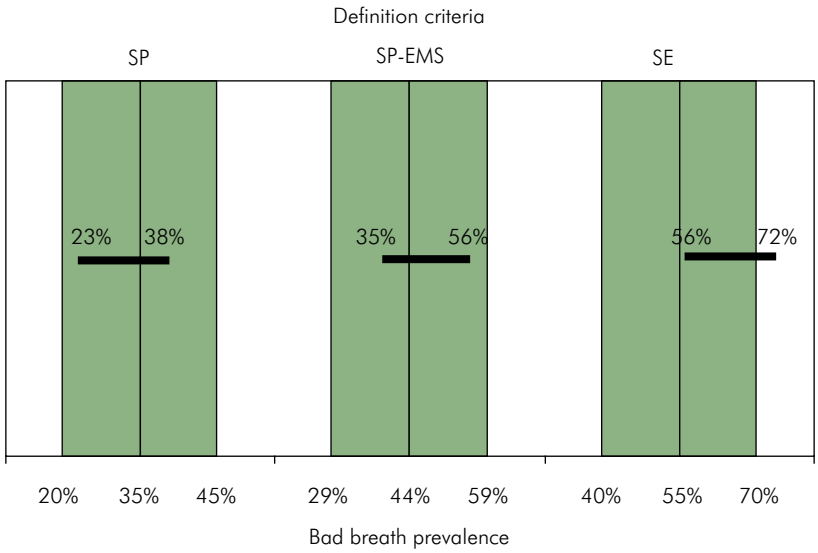
Variable	Unadjusted PR	Unadjusted 95%CI	Adjusted PR	Adjusted 95%CI
Bad breath (SP definition)				
Dyspepsia	0.87	0.63–1.20	0.98	0.88 – 1.10
Male	1.04	0.78–1.40	1.02	0.91–1.15
Age	1.16	0.97–1.40	1.00	0.99 –1.01
Bad breath (SP-EMS definition)				
Dyspepsia	1.11	0.79–1.56	1.04	0.77–1.40
Male	1.15	0.85–1.56	1.17	0.86–1.59
Age	1.11	0.91–1.34	1.00	0.99 –1.01
Bad breath (SE definition)				
Dyspepsia	1.00	0.99–1.01	1.16	0.96–1.39
Male	1.00	0.99–1.01	1.10	0.91–1.34
Age	1.00	0.99–1.00	1.00	0.99 –1.00

PR: Prevalence ratio (Log-binomial model); CI: confidence interval; SP: specific cutoff point: very severe or severe vs. moderate or mild or absent halitosis (n = 308); SP-EMS: specific cutoff point excluding moderate score: very severe or severe vs. mild or absent halitosis (n = 228); SE: sensitive cutoff point: very severe or severe or moderate vs. mild or absent halitosis (n = 308).

Table 4. Equivalence hypothesis test of the proportion of bad breath in the dyspepsia (exposed) and comparison (unexposed) groups in adults evaluated in the morning after a 12-hour fasting period.

Bad breath definition criteria	95%CI		p-value
	LB	UB	
Bad breath (SP definition)			
(H_0: P_E - $P_{\bar{E}}$ = 0) *vs.* H_A: diff ≠ 0			0.46
(H_0: P_E - $P_{\bar{E}}$ ≤ 0) *vs.* H_A: diff > 0			0.77
(H_0: P_E - $P_{\bar{E}}$ ≥ 0) *vs.* H_A: diff < 0			0.23
Difference between proportions		-0.16	0.06
95% CI of the equivalence test:	-0.13	0.04	
Equivalence for delta = ± 0.15			0.03
Bad breath (SP-EMS definition)			
(H_0: P_E - $P_{\bar{E}}$ = 0) *vs.* H_A: diff ≠ 0			0.87
(H_0: P_E - $P_{\bar{E}}$ ≤ 0) *vs.* H_A: diff > 0			0.44
(H_0: P_E - $P_{\bar{E}}$ ≥ 0) *vs.* H_A: diff < 0			0.56
Difference between proportions	0.02	-0.11	0.16
95% CI of the equivalence test:	-0.09	0.13	
Equivalence for delta = ± 0.15			0.03
Bad breath (SE definition)			
(H_0: P_E - $P_{\bar{E}}$ = 0) *vs.* H_A: diff ≠ 0			0.14
(H_0: P_E - $P_{\bar{E}}$≤ 0) *vs.* H_A: diff > 0			0.07
(H_0: P_E - $P_{\bar{E}}$ ≥ 0) *vs.* H_A: diff < 0			0.93
Difference between proportions	0.09	-0.03	0.20
95% CI of the equivalence test:		-0.00	0.18
Equivalence for delta = ± 0.15			0.14

CI: confidence interval; LB:= lower bound of the CI; UB: upper bound of the CI; H_0: null hypothesis; H_A: alternative hypothesis; PE; proportion of exposed participants; PĒ: proportion of unexposed participants; diff: difference; SP: specific cutoff point: very severe or severe vs. moderate or mild or absent halitosis (n = 312); SP-EMS: specific cutoff excluding moderate score: very severe or severe vs. mild or absent halitosis (n = 231); SE: sensitive cutoff point: very severe or severe or moderate vs. mild or absent halitosis (n = 312).



SP: specific cutoff point: very severe or severe vs. moderate or mild or absent halitosis (n = 312); SP-EMS: specific cutoff excluding moderate score: very severe or severe vs. mild or absent halitosis (n = 231); SE: sensitive cutoff point: very severe or severe or moderate vs. mild or absent halitosis (n = 312).

Figure 2. Distribution of the 95% confidence intervals of bad breath prevalence among patients with dyspepsia (horizontal thick black lines) concerning bad breath prevalence in the comparison group (x-axis) within an equivalence margin of ± 15% (grey bars), according to three definitions of bad breath (two specific, SP, and SP-EMS, and one sensitive, SE) in adults evaluated in the morning after a 12-hour fasting period.

breath leads to a specific demand for gastroenterology services. One study reported that 57% of patients with gastrointestinal disorders had bad breath and that 60% of the disorders affected the stomach (unrelated to *H. pylori*), followed by the duodenum and esophagus.[8] Another study, however, reported that *H. pylori* infection was detected in 91% and 32% of patients with and without bad breath, respectively.[6]

The present study detected *H. pylori* infection in 49% of patients with dyspepsia. Studies have reported a relationship between halitosis and *H. pylori* infection.[6,12] A study performed on children detected *H. pylori* in 83% of participants with dyspepsia. The study found an association between the presence of the bacterium and dyspepsia.[31] Another study on adults with dyspepsia showed that *H. pylori* is often present in individuals with gastritis.[32] The frequency of *H. pylori* in patients with and without dyspepsia was 75.5% in a Venezuelan study, *i.e.*, no difference was found between the prevalence of *H. pylori* infection in patients with and without dyspepsia.[33]

We found no association of bad breath with sex or age, either in the bivariate or in the adjusted analysis. A previous study carried out with families of university students in Rio de Janeiro has found that halitosis was associated with sex (prevalence of 21% and 9% in men and women, respectively) and with age (prevalence of 17% and 7% in age groups "≥ 20" and "< 20", respectively).[1] These findings, which are at odds with those of the present study, may be explained by the differences in the profile of the participants. In our study, only 2% of the participants were aged less than 20 years, while in the aforementioned study, 21% were younger than 20 years.[1]

Oral activity during food and liquid intake promotes self-cleaning of the tongue and oral mucosa, stimulates salivation and, consequently, reduces the risk of bad breath. On the other hand, prolonged fasting intensifies bad breath.[34] The risk of bad breath is higher in the morning.[35,36] Considering these factors, in our study, we selected patients who had fasted for 12 hours for the morning evaluations. This procedure also contributes to increasing the sensitivity of the assessment of the presence of bad breath. For these reasons,

we expected to find (and we actually found) a high prevalence of bad breath.

To avoid inter-observer variability, which is an important limitation of subjective measures, the evaluation of bad breath was performed by a single evaluator (NCPR). And as pointed out by the literature, organoleptic measurement by a trained professional is standard practice in studies on bad breath.[37-40]

Still in the context of the limitations of the study, considering that knowledge of the presence of dyspepsia in a given participant could influence the observer's assessment of the participants' breath by giving them a worse score, we blinded the observer during the breath measurement of the patients and of their chaperones so that the observer would not know who the patient with dyspepsia was and who the chaperone was. However, it was not possible to use the same strategy in the comparison group because the presence of a chaperone was not mandatory during the routine examinations at the clinical analysis laboratory. This may have introduced differential information bias in that the blinding of the evaluator was performed only in the dyspepsia group. Two possible information biases may have occurred: a) underestimation of the prevalence of bad breath in the comparison group, considering that the evaluator may have been more tolerant of (less alert to) patients without dyspepsia so that they received better scores and b) overestimation of the prevalence of bad breath in the comparison group because of the equality of the prevalence of bad breath in the two groups. The rater may have been less tolerant of (more alert to) breath odor, giving the comparison group worse scores to counterbalance the effect of dyspepsia on breath odor. It is also possible that some of the participants in the comparison group had dyspepsia, given that the comparison group was made up of patients from different hospital sectors, without excluding patients with dyspepsia. However, we believe that the risk of information bias in this group is low, as the outcome assessor did not know which patients had dyspepsia. Another limitation is the fact that the comparison group came from a different hospital than the group with dyspepsia. Even though a comparison group from another hospital was used, the two hospitals that participated in the study were university hospitals located in adjacent neighborhoods, whose coverage extends to the general population of the city of Rio de Janeiro. Thus, we believe that the two groups were similar in geographic, socioeconomic, and demographic characteristics. However, we cannot rule out the possibility of differential access to the two sectors investigated–the endoscopy unit and the clinical pathology laboratory. The sector for data collection from the comparison group was specifically chosen because we could then collect data from fasting patients and from the dyspepsia group at the clinical pathology laboratory. Finally, considering the popular belief that bad breath is associated with digestive pathologies, we should expect to find a larger amount of people complaining about bad breath in the gastroenterology outpatient clinic than in the clinical pathology sector. Anticipating the possible introduction of this selection bias, a question was inserted in the questionnaire to identify why the patient sought care at the clinic. Contrary to what we expected, only two participants reported that they sought the gastroenterology outpatient clinic because of bad breath. Thus, the possibility of introducing this bias was unlikely. Furthermore, although there may have been a greater chance of selectively finding more patients with bad breath in the gastroenterology outpatient clinic than in the comparison group, this selection bias would overestimate the prevalence of bad breath in patients with dyspepsia, which would make it more difficult to confirm our equivalence hypothesis.

As a strength of this research, the findings indicate that the prevalence of halitosis does not differ between individuals with and without dyspepsia. This finding can guide clinicians and gastroenterologists through the care of patients with bad breath, whether by establishing the appropriate treatment or by referring them for exams and to other specialists.

Conclusions

The use of two forms of analysis (association and equivalence) was a promising strategy, providing more elements to test our hypothesis. New studies, involving other populations, other designs, and a more significant number of participants can contribute

to elucidating the role of gastric problems in the prevalence of bad breath.

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